MAY-JUNE 2002 • VOLUME 24, NUMBER 3

Consent for Continuing Research Participation

What Is It and When Should It Be Obtained?

BY DAVE WENDLER AND JONATHAN RACKOFF

Many commentators have argued that informed consent should not be a single event at which subjects are informed and their consent obtained, but rather a process that continues for the duration of subjects' research participation.[1] Some have argued that investigators should also obtain consent for continuing participation of subjects who participate in research for an extended period.[2] And federal regulations recognize the importance of continuing consent, directing institutional review boards (IRBs) to consider whether the initial consent process should include a statement that subjects will be provided with "significant new findings developed during the course of the research" (45 CFR 46.116). Yet neither the regulations nor the research ethics literature explain how to implement informed consent as a process rather than an event.

The present paper attempts to fill this lacuna by developing a systematic analysis of "continuing" consent: why it's important; how and when it should it be solicited; what information it should include; and how subjects should indicate their ongoing willingness to participate. Because the answers to these questions vary depending on the reasons for obtaining subjects' continuing consent in specific cases, we distinguish four types of continuing consent: (1) reconsent, (2) ongoing consent, (3) reaffirmation of willingness to participate, and (4) dissent.

Why Is "Continuing" Consent Important?

The elements of informed consent—the factors relevant to individuals' decisions whether to participate in research—can be divided into three categories: (a) the nature of the research itself, as determined by its purpose, risks, potential benefits, requirements, and alternatives; (b) the individual's personal and medical situations; and (c) the individual's preferences and interests. When these factors remain constant, individuals' initial consent can be considered durable. That is, in the absence of any expressions of doubt, it can be assumed that subjects are willing to continue to participate. However, when subjects participate in research for extended periods of time, these factors may change unexpectedly.[3] When this happens, the fact an individual gave initial consent should not be taken to imply that she is willing to continue to participate given these changes.

Subjects' medical situations sometimes change over the course of their research participation (tumors metastasize or clinical depression gets worse, for exam-

Dave Wendler and Jonathan Rackoff, "Consent for Continuing Research Participation: What Is It and When Should It Be Obtained?" *IRB: Ethics & Human Research* 24 No. 3 (2002): 1-6.

ple), calling into question whether research participation remains in these participants' best interests. Similarly, the nature of the research itself may change, as happens when an investigator changes the purpose of a longitudinal survey by adding a new series of questions. It also appears that individuals sometimes do not fully understand the protocols to which they initially consent. Part of the problem is that research can be complicated, to the point that individuals may not fully understand the research in one, or even several meetings with the research team.

Finally, individuals often cannot fully understand a research protocol until after they have experienced the procedures it involves. For example, individuals who consent to a series of lumbar punctures are likely to understand the protocol better, because they more fully appreciate the nature of its interventions, after they have undergone the first few lumbar punctures.

To address these concerns, investigators should periodically obtain the continuing consent of subjects who participate in research for an extended period of time. Moreover, when reviewing studies that propose to enroll subjects for an extended period, IRBs should review and approve the investigator's plans for obtaining subjects' continuing consent.

Reconsent

The primary purpose of soliciting subjects' continuing consent is to ensure that research participation is consistent with their contemporaneous preferences and interests. This suggests that investigators should solicit subjects' continuing consent whenever there is sufficient reason to think that this may no longer be the case. In general, whether individuals are willing to participate in research and whether participating is in their interests, is largely a function of the purpose, risks, potential benefits, and requirements, and what alternatives there may be to participating. It follows that investigators should ask subjects to renew their consent whenever there are material and significant changes in the research's purpose, risks, potential benefits, requirements, or alternatives.

The standard for determining whether a change is "material" to individuals' continuing research participation, we suggest, should be similar to the standard for determining whether information is material to participants' initial decision to enroll. Hence one way for investigators and IRBs to determine whether subjects already participating in a study should be informed of a change in one of the elements noted above is to ask whether this information would be relevant at initial consent.

For changes that are not material, the answer will be "no"—for instance, using a different laboratory to analyze biological samples or adding a question about exercise practices to a longitudinal survey of health status. To make an informed decision whether to enroll in the research, subjects need not know which company will do the sample analysis or precisely which questions will be included in the survey, and IRBs would not normally require that this information be conveyed at the time of enrollment. On this "initial consent" test it follows then that investigators need not inform participants of these kinds of changes in the research after they have already enrolled.

Material changes, in contrast, will be found relevant on the initial consent test. Material changes can be categorized as either significant or not significant. Significant material changes, such as discovery of a serious new side effect, likely would affect whether participation is consistent with subjects' preferences and interests. In contrast, material but not significant changes—for instance, discovery of a minor new side effect—would not be likely to affect an individual's decision to enroll.

In addition to the research itself, changes in individuals' medical or personal situations may also be material and significant. This is often easy to determine. For instance, whether continued participation in a cancer chemotherapy trial is in an individual's interests may depend on whether her cancer is in remission or on the severity of her prognosis. Similarly, an individual's willingness to continue to participate in an epidemiological study may be affected by the development of a terminal cancer.

Investigators typically do not need to inform subjects of these changes or solicit their continuing consent—participants themselves are in the best position to assess the impact of personal changes and decide whether to withdraw or to continue. There is an important exception to this rule, however. In the process of conducting research, investigators may become aware of changes in subjects' medical or psychological situations that are material and significant that the individuals themselves are not aware of—for example, that their viral burden has increased or their depression has gotten worse. When these changes do not disqualify participants from remaining in a study altogether, investigators should inform them of the changes and confirm their willingness to continue to participate.

Because reconsent involves soliciting subjects' continuing consent in light of material and significant changes, it should not be obtained in a haphazard manner—for instance, by a clinic nurse during a scheduled examination. The process should be formalized along the lines of the current process of initial consent solicitation.

Further, a responsible physician should inform the IRB of the

TABLE: THE FOUR TYPES OF CONTINUING CONSENT

	When Solicited	How Solicited	Information Provided	How Indicated
Reconsent	Whenever there are "material" and "significant" changes in the research's purpose, risks, potential benefits, requirements, or alternatives.	By a responsible investigator; in a dedicated meeting; with documentation and an independent witness	The specific change(s), as well as any aspects of protocol affected by the changes	Same as initial consent; signature not mandatory
On-Going Consent	Whenever there are material, but not significant changes in the research's purpose, risks, potential benefits, requirements, or alternatives	By a responsible investigator; with documentation, but not an independent witness	Nature of the specific change(s)	Verbal agreement; signature inappropriate
Reaffirmation of Willingness to Participate	Approximately every two months of continuous research participation; at time of recontact for research involving extended breaks	By any team member; as part of regularly scheduled interactions; documentation and witness unnecessary	Nature and importance of research, upcoming procedures, right to withdrawal	Verbal agreement; signature inappropriate
Dissent	Entire team should monitor subjects throughout their research participation	Not actively solicited	Team members should remind subjects they are involved in research and free to withdrawal	Body movements, expressions, verbal statements

A "material" change is a change that is relevant to whether research participation is consistent with subjects' preferences and interests.

A "substantial" change is a change that has a reasonable likelihood of affecting whether research participation is consistent with subjects' preferences and interests.

changes triggering reconsent, explain why it nonetheless makes sense to continue the subject in research, and obtain the IRB's approval for the specific wording that will be used to inform the subject. The IRB should be asked to approve a written form when reconsent is deemed appropriate. Once IRB approval is obtained, a responsible investigator should inform the subject of the changes orally and in writing during a session dedicated to this purpose.

Investigators and IRBs should be aware that some material and significant changes have implications for other aspects of subjects' research participation. Progression of an individual's depression, for instance, may make participation in a placebo-controlled treatment trial riskier or may alter the clinically relevant alternatives to participating in such a trial. In such cases, investigators should explain the alternatives to research participation, as well as the potential benefits (even if those have not changed) so that subjects can assess the protocol's overall risk/benefit profile afresh in light of the changes in their personal circumstances.

Like initial consent, subjects' oral or written reconsent should be witnessed by at least one individual who has no conflict of interest relevant to the decision to continue research participation. Members of the research team are not appropriate witnesses in this context. Family members are usually independent of the research team, but not always sufficiently disinterested to be appropriate witnesses. Other health care professionals—clinic nurses or social workers, for example—or members of the community might serve as independent witnesses. Institutions and IRBs should develop explicit policies identifying who may serve as witnesses for purposes of

reconsent. Institutions that have a policy for witnessing initial consent may want to simply apply it to continuing consent as well. When material and significant changes produce an emergent situation, the investigator should request timely approval, or stop the subject's research participation until approval for reconsent is obtained. IRBs should establish a mechanism for rapid approval, or a mechanism that allows investigators to provide subjects with clinically indicated treatments until the request for continued research participation is reviewed. Finally, if a protocol is still enrolling subjects, material and significant changes in the protocol itself should be reflected in an appropriately updated initial consent form and conversation.

Ongoing Consent

Some changes, although material to subjects' research participation, are not significant in that they are very unlikely to affect whether individuals who previously agreed to enroll are willing to continue to participate. Such material, but nonsignificant changes might include expanding the goals of a longitudinal survey by adding a new series of questions or learning that the study drug has a hitherto unknown but relatively minor side effect, such as sore throat for a few hours. While such changes in the purpose or risks of research are clearly material to subjects' participation, they do not seem to require reconsent. Instead, a responsible investigator should inform subjects of these changes and solicit their "ongoing" consent.

Since ongoing consent is solicited in response to material changes that are unlikely to affect subjects' willingness to participate, the process need not be formalized in the manner of reconsent. Most importantly, soliciting subjects' ongoing consent does not seem to require either a special session dedicated to this purpose or an independent witness. Instead, the investigator can solicit ongoing consent as part of her regular interactions with subjects. Subjects need not be informed of these changes in writing, though the research record (or perhaps the individual's medical record) must document that the subject has been orally informed and has provided ongoing consent. As with changes in the protocol that merit reconsent, the IRB should consider whether material, but nonsignificant changes in the protocol should be reflected in changes to the initial consent form for newly enrolled participants.

Reaffirmation of Willingness to Participate

Sometimes individuals' preferences and interests change over time even in the absence of material changes in the research protocol or their own situations. For instance, some individuals may decide they want to pursue other projects with their time rather than participate in research. Of course, the more time that elapses between individuals' last agreement to participate and their present participation, the greater the possibility that the prior decision no longer reflects their current preferences and interests. In these circumstances, a less formal means of ensuring that subjects remain willing participants than either reconsent or ongoing consent seems appropriate. As the interval between the most recent expression of agreement and present research participation increases, the possibility that subjects' interests have changed becomes sufficiently great that investigators should solicit "reaffirmation" of their continued willingness to participate.

Investigators who interact with subjects every day or several times a week may already be regularly assessing their willingness to continue to participate, and IRBs may deem the practice sufficient for the purpose of obtaining subjects' reaffirmation. With that said, however, investigators should not simply take individuals' lack of positive objections as indicative of continued willingness to participate. Instead, investigators should explicitly remind subjects that they are in research and are free to withdraw, and actively assess their willingness to continue to participate.

Because there are no material changes to convey, reaffirmation should be informal and straightforward: The investigator should simply thank subjects for their participation, remind them of the importance of the research, briefly explain any upcoming procedures, and remind them of their right to withdraw. In our view, the absence of new information suggests that it would be inappropriate to ask subjects to reaffirm their willingness to participate by signing a form. Instead, investigators should simply ask for subjects' oral reaffirmation, or ask them to indicate any concerns or hesitations they might have about continuing to participate. Similarly, there seems no need for independent witnesses of subjects' reaffirmation, and no need to provide them with written information.

Determining how often to solicit reaffirmation requires balancing two competing considerations: inappropriately giving the impression that circumstances have changed significantly, versus uncritically accepting subjects' initial consent for the duration of the research. In general, we assume that individuals' preferences and interests remain constant over short periods of time—if I agree to participate in research today, it's reasonable to assume that I am willing to participate tomorrow (provided my situation and the research remain essentially unchanged). Asking subjects to reaffirm their willingness to participate every day, or even every week, may inadvertently convey the impression that significant changes in the protocol or the subject's condition have

occurred, potentially confusing subjects and diminishing their understanding. To help mitigate this risk, investigators should inform prospective subjects that re-affirmation of consent will be solicited at regular intervals during their research participation. At the other extreme, accepting individuals' initial agreement for the duration of their research participation, no matter how long it lasts, is likely to result in individuals participating in research that is no longer consistent with their preferences and interests.

Unfortunately, there are no data on how frequently subjects' research preferences and interests change. Until such data are collected, institutions and IRBs will have to set standards based on their own educated guesses. Our sense is that soliciting reaffirmation of subjects' willingness to participate more frequently than once a month would be too often, but soliciting it any less frequently than every 6 months would be too infrequent. For sake of discussion, for studies in which investigators interact with subjects on a regular basis, we suggest that subjects' reaffirmation be solicited approximately every two months. Thus absent any material changes, investigators who conduct studies that last less than two months need not solicit reaffirmation of subjects' willingness to participate.

Rather than insisting on a strict schedule of soliciting reaffirmation at precisely two-month intervals, however, IRBs should take advantage of natural transitions in a given study to invite subjects to reaffirm their willingness to participate. Some studies, such as drug treatment studies that involve distinct cycles or longitudinal surveys that involve recurring sessions, are structured in distinct phases. In these cases, whichever member of the research team is involved at that point in the study could solicit subjects' reaffirmation at the beginning of the cycle or session closest to two-month intervals. Similarly, for studies of longer duration that involve a series of procedures, the investigators could explain the individual procedures in turn, and ensure, based on this explanation, that the subjects are still willing to undergo them.

For some research, particularly epidemiology and survey research, investigators may have contact with subjects only very infrequently, perhaps no more than once a year, rendering it impossible to solicit their reaffirmation more frequently. In these cases, investigators should solicit subjects' reaffirmation at the next research contact. After long periods without contact, subjects may forget important aspects of their research participation. Moreover, there is an increased chance that subjects' preferences and interests may have changed. The process of soliciting subjects' reaffirmation after an extended break should thus include a very brief summary of the study. For low risk studies, a few minutes devoted to outlining the purpose of the research and the procedures involved should be sufficient.

IRBs should take advantage of natural transitions in a given study to invite subjects to reaffirm their willingness to participate.

Whenever a year or more passes between research contacts, or the risks of the study are greater than minimal, the reviewing IRB should consider whether a more formal and rigorous process is warranted. One possibility would be to require that the investigator develop a one-page summary to provide to subjects at the time of renewed research contact. In considering this possibility, IRBs should clearly distinguish providing a written summary from requiring that subjects sign the summary. Because reaffirmation is solicited from subjects who have already consented and been involved in the research and there have been no material changes in the nature of their participation, there is no need for them to indicate their reaffirmation by signing the written summary.

Dissent

Between solicitations of reaffirmation, subjects should be considered willing to continue to participate unless they explicitly object to doing so. Of course, lack of dissent should be regarded as evidence of ongoing willingness to participate only when subjects are fully informed and have the opportunity to express disagreement. Thus the process of dissent should be continuous throughout individuals' research participation. Investigators should regularly remind subjects that they are participating in research and have the right to withdraw. And as part of their regular interactions with subjects, the entire research team should monitor subjects for any indications of dissent.

Investigators have an obligation not to engage individuals in research when there are reasons to believe they do not want to participate. Requiring that individuals indicate their dissent by providing a signature, or even requiring that they express their dissent orally, inappropriately puts the burden on subjects. Instead, the research team should be alert to any signs suggesting that an individual no longer wants to participate, whether in speech or in behavior (such as pulling an arm away during a blood draw).

Respect for subjects' autonomy and dignity does not require that subjects be removed from research at the first sign of dissent, however. Because dissent is not necessarily always expressed verbally, team members may misconstrue certain

actions as dissent. And some expressions of dissent may reflect momentary reactions by subjects rather than sustained preferences. Even the most committed research subjects may flinch at a blood draw, be reluctant to undergo a lumbar puncture, tire of answering survey questions, or have a passing wish to go home.

To avoid misinterpreting subjects' words or behavior, research teams should develop a plan for how they will follow up on any signs of apparent dissent. The first step may simply be to pause and ask the subject if she or he is okay and ready to proceed. If the subject gives further indications of dissent, an appropriate team member should explicitly address whether the subject is willing to continue participating. In some cases, reassurance may be all that is needed; in others, a short postponement of the procedure may be sufficient.

One of the most difficult dissent scenarios involves a subject who strongly wants to participate in a given research study, but is unwilling to undergo a specific procedure. To anticipate these situations, and avoid inconsistent decisions across subjects, the research team should distinguish required from optional procedures. In some cases, it may be possible to skip the lumbar puncture, or allow the subject to complete a questionnaire at home rather than in the clinic or office. In other cases, the procedure in question will be necessary for scientific reasons. Although it may help to explain why the procedure is necessary, subjects who are unwilling to undergo required procedures will have to be excused from further participation in the research.

Ambivalent subjects, who repeatedly express and then withdraw indications of dissent, present a second difficulty. Since such subjects may simply be unwilling to tell the research team outright that they wish to withdraw, it may make sense to obtain an independent assessment of their willingness to continue to participate. In the end, the default should be that individuals are not continued in research unless there is convincing reason to believe that they want to participate. When it is ultimately unclear whether a subject really is dissenting or not, he or she should be removed. However, these decisions should be made carefully, particularly when participation offers subjects a chance for medical benefit that is unavailable outside the research context.

Acknowledgments

Thanks to Neal Dickert, Frank Miller, Christine Grady, Ezekiel Emanuel, and Robert Levine for their helpful suggestions.

The ideas and opinions expressed are the authors' own. They do not represent any position or policy of the National Institutes of Health, Public Health Service, or Department of Health and Human Services.

■ **Dave Wendler, PhD,** is head of the unit on vulnerable populations in the Department of Clinical Bioethics; **Jonathan Rackoff, BA,** is a fellow at the Department of Clinical Bioethics, National Institutes of Health, Bethesda, Md.

References

1. See, e.g., Geller G, Strauss M, Bernhard BA, Holtzman NA. Decoding informed consent: insights from women regarding cancer susceptibility testing. *Hastings Center Report* 1997;27(2):28–33.

2. See ref. 1, Geller et al. 1997.

3. Subjects may consent to anticipated changes at the time of initial consent. Of course, this doesn't preclude the possibility that experiencing these changes may lead subjects to change their minds.

4. For a discussion of the difficulties in requiring subjects to indicate consent by means of a signature, see Wendler D, Rackoff J. Respecting individual autonomy: What's a signature got to do with it? *IRB* 2001;23(3):1–4.